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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/380,327	09/03/99	ROBERTSON S	A20-005

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EXAMINER
HUYNH, P

ART UNIT	PAPER NUMBER
1644	6

DATE MAILED: 03/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/380,327	ROBERTSON ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-97* is/are pending in the application.

4a) Of the above claim(s) *63, 72, 74, 78, 80, 82-83, 92, 94-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group XII (Claims 50-60, 70-71, 73, 76-77, 79, 81, 83-88 and 90-93) and species reading on paternal sperm antigen and active form of TGFβ2 in Paper No. 5 is acknowledged. The traversal is on the grounds that the claimed subject matter of Group I-XXX directed to a method of treating infertility in a human by administering various forms of TGFβ including (TGFβ1, TGFβ2, TGFβ3 and activin) with various antigens including sperm antigen, MHC class I antigen and antigen on the conceptus) are not distinct since they are classified in the same class and subclass and would not place an undue burden on the Examiner when examined simultaneously. This is not found persuasive because of the reasons set forth in paper No. 4, mailed 11/27/00. While a search of the different inventions may be overlapping they are not co-extensive and a thorough and proper search of all the inventions concurrently would pose an undue burden on the Examiner.

Consistent with the International Search Report and the reasons set forth in paper No. 4, mailed 11/27/00, the invention of Group I was found to have no special technical feature over the prior art. Feinberg *et al.* ('825) teach the use of transforming growth factor beta (TGFβ) to treat infertility in a human or mammal prior to conception. Feinberg differs from the claimed invention by not combining the use of male antigen from the prospective father.

Chaouat *et al.* teaches immunizing infertile female mice with paternal MHC class I antigen to improve infertility

Toder *et al.* teaches immunization of infertile women with paternal or third party leukocyte antigen to reduce spontaneous abortion.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

Upon further reconsideration, the examiner has agreed to include claims 61-62, 68-69, and 75 as far as it reads on MHC class I antigen on sperm cells. The requirement is still deemed proper and is therefore made FINAL.

Claims 50-97 are pending.

Claims 50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93 reading on sperm antigen and active TGFβ2 are being acted upon in this Office Action.

Claims 63, 72, 74, 78, 80, 82-83, 92, 94-97 and claims that read on group of TGFβ1, TGFβ3 and activin are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

2. Applicant should amend the first line of the specification to indicate the status of the priority documents, i.e., This application is a 371 of PCT AU98/00149 filed 3/6/98. See MPEP 1302.04.

3. The drawings, filed on 9/3/99, are not in compliance with 37CFR 1.84(a). Please see attached PTO 948. Appropriate correction is required.

4. Appropriate correction is required in the specification. See page 15, The brief description of the drawings for Fig 8, "intra-uterine infusion with CBA sperm in the presence of absence **of** 10ng rTGFβ1". It should be "or". The legend on the X axis of Fig 1B, Fig 5, Fig 6 and Fig 8A and B are not clear. See page 7 line 7 "one or more antigen" and page 21 line 4 "370C". It should be "one or more antigens" and "37°C", respectively.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TGFβ1 to treat infertility condition in mammals, does not reasonably provide enablement for any "analogs" thereof including TGFβ2, TGFβ3 and activin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Claims 50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93 recite "an effective derivative or analogs thereof". The specification as filed does not teach all the possible analogs of TGFβ that after substitution or deletion of a peptide will maintain both the structural limitation and functional limitation of TGFβ. Although the function of TGFβs appear to be overlapping and converging on the TGFβ receptor and the signaling transduction factors SMAD2 or SMAD3, the state of the prior art is such that the functions of TGFβ1, TGFβ2, TGFβ3 and analogs thereof including activin and inhibin are distinct and largely nonoverlapping based on targeted disruption of the three TGFβ genes (See Dunker et al., Eur J Biochem 267(24): 6982-8). The state of the art is that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable for analogs (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Furthermore, the specification does not reasonably provide enablement for any "effective derivative or analogs thereof" other than TGFβ1. There are insufficient working examples to established any of the claimed effective derivative or analogs thereof, including TGFβ2, TGFβ3 and activin for treating infertility. Further, the specification as filed discloses that "the specificity of TGFβ to be co-administered with the male antigens is at present not entirely clear, and because TGFβ1 is thought to be responsible whereas TGFβ2, TGFβ3 are less important, it is more likely that TGFβ1 is to be used" (See page 9 line 7-9). Likewise, there is a lack of working examples for TGFβ2 and analogs thereof. Thus, the specification as filed fails to provide guidance regarding what modification from the disclosed TGFβ protein would result in an analog that is functionally biologically active in treating infertility in the female.

In view of the lack of working examples for TGFβ analogs including TGFβ2, TGFβ3 and activin, the unique functions of each TGFβ protein within a given tissue and the lack of guidance with respect to appropriate modifications of the disclosed TGFβ, the specification disclosure is

insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

8. Claims 50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The instant claims 50-62, 64-71, 73, 75-77, 79, 81, 84-91, 93 are drawn to "TGFβ derivative and analogs thereof" that are effective in treating infertility in female. There is insufficient written description to show that Applicant was in possession of any effective derivative or analogs of TGFβ that are effective in treating infertility in female as filed. Since only the effect of TGFβ1 is provided, the derivative or analogs of TGFβ is not adequately described. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119F.3d 1559, 43 USPQ2d 1398.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 50-60, 70-71, 73, 76-77, 79, 81, 83-88 and 90-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50-60, 70-71, 73, 76-77, 79, 81, 83-88 and 90-93 are indefinite in the recitation of "derivative or analogs thereof" because the metes and bounds of such conditions are ambiguous and unclear.

Claims 64 and 65 are indefinite because the claims are being a substantial duplicate thereof.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 50-54, 58-65, 61-62, 66, 73, 76-77, 84-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feinberg *et al.* (US Pat No. 5,395,825, May 1995; IDS, See entire document) in view of Gafter *et al.* (J. of Clinical Immunology 17(5): 408-419, 1997; IDS, See entire document).

Feinberg *et al.* ('825) teaches a method of treating infertility by administering TGFβ, wherein said TGFβ can be TGFβ2 (See column 5, line 9-11, in particular) to a female as a method of fertility therapy by increasing the success rate of implantation (See column 5 line 9-12). The TGFβ2 may be administered either before, after or simultaneously with the male antigens, including sperms of the prospective father which are known to express MHC class I molecule and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female as encompassed by instant claims 50-54, 58-65, 66, 73, 76-77, 84-85, (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21). Furthermore, TGFβ or analog may be administered by injection, patch, gels and in the form of platelets (See column 5, line 1-2; column 6, line 45-55).

Feinberg *et al.* differs from the claimed invention by not using leukocyte antigen containing MHC class I molecule as a source of paternal antigen.

Gafter *et al* teaches a method of treating infertility in a human or mammal by immunizing the female with one or more paternal leukocyte antigens prior to conception. Administration of leukocyte antigen has led to an increase in TGFβ while the production of various Th1 cytokines, including IL-2, INFγ, IL-12, pro-inflammatory cytokines such as IL-1, TNFα, IL-6 were decreased. TGFβ has been shown to inhibit a variety of immune responses including NK and LAK activities. TGFβ is an "effective analog" of TGFβ2 and is present in seminal fluid and increase in uterine tissue during pregnancy. An increase of TGFβ would lead to immune modulation/suppression of cell-mediated immune responses of the female host resulting in immune tolerance toward the conceptus and maintenance of pregnancy encompassed by claims 50-51, 61-63, 66, (See page 408 right column, last paragraph; page 411, cytokine secretion, Figs 1-3 in particular; page 412 1st paragraph and Fig 4).

Therefore, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to combine TGFβ and paternal antigens as a method of treating infertility because TGFβ and allogeneic immunization of paternal antigen will synergistically enhance the survival of the fetus.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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March 8, 2001

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